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In re application of: Toshiaki TAGAWA et al. Attorney Docket No. P21620

Application No. : 09/926,358 Group Art Unit : 1615

Filed : January 7, 2002 Examiner : Kishore

For : LIPOSOME BONDED WITH ANTIBODY AND POLYALKYLENE GLYCOL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Appeal Brief-Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

Transmitted herewith is an **Appeal Brief under 37 C.F.R. § 41.37** in the above-captioned application.

____ Small Entity Status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a previously filed statement.

_X_ Exhibit 1.

____ A Request for Extension of Time.

____ No additional fee is required.

The fee has been calculated as shown below:

Claims After Amendment	No. Claims Previously Paid For	Present Extra	Small Entity		Other Than A Small Entity	
			Rate	Fee	Rate	Fee
Total Claims: 14	*20	0	x25=	$	x 50=	$ 0.00
Indep. Claims: 1	**3	0	x100=	$	x200=	$ 0.00
Multiple Dependent Claims Presented			+180=	$	+360=	$ 0.00
Extension Fees for ____ Month(s)				$		$ 0.00
Appeal Brief Filing Fee						$500.00
* If less than 20, write 20 ** If less than 3, write 3			Total:	$	Total:	$500.00

____ Please charge my Deposit Account No. 19-0089 in the amount of $_____.

_X_ A check in the amount of $500.00 to cover the filing fee is included.

_X_ The U.S. Patent and Trademark Office is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 19-0089.

_X_ Any additional filing fees required under 37 C.F.R. 1.16.

_X_ Any patent application processing fees under 37 C.F.R. 1.17, including any required extension of time fees in any concurrent or future reply requiring a petition for extension of time for its timely submission (37 C.F.R. 1.136(a)(3)).

Bruce H. Bernstein
Reg. No. 29,027

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Toshiaki TAGAWA et al.

Appl No : 09/926,358

Filed : January 7, 2002

For : LIPOSOME BONDED WITH ANTIBODY AND POLYALKYLENE GLYCOL

Group Art Unit: 1615

Examiner: Kishore

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Appeal Brief-Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

This appeal is under 35 U.S.C. 134 from the decision of the Examiner finally rejecting claims 10-12 and 15-24 and 26-37 as set forth in the Final Office Action of November 15, 2005.

A Notice of Appeal in response to the November 15, 2005 Final Office Action was filed on March 15, 2006, so that the initial due date for filing the Appeal Brief is May 15, 2006.

The requisite fee under 37 C.F.R. 41.20(b)(2) in the amount of $500.00 for the filing of the Appeal Brief is being paid by check, submitted herewith. However, if for any reason the necessary fee is not associated with this file, authorization is hereby provided to charge the fee for the Appeal Brief and any necessary extension of time fees to Deposit Account No. 19 - 0089.

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(I) REAL PARTY IN INTEREST

The real party in interest is Mitsubishi Chemical Corporation by an assignment from the inventors recorded on January 7, 2002 at Reel 012434, Frame 0597.

(II) RELATED APPEALS AND INTERFERENCES

None.

No related appeals and/or interferences are pending.

(III) STATUS OF THE CLAIMS

Claim 1-15, 24-31, 35 and 36 are canceled.

Claims 16-23, 32-34 and 37 stand finally rejected.

(IV) STATUS OF THE AMENDMENTS

An Amendment Under 37 C.F.R. 1.116 was filed February 15, 2006.

The Advisory Action mailed March 6, 2006 indicated that the request for reconsideration has been considered but does NOT place the application in condition for allowance; however, the Advisory Action did not indicate whether or not the Amendment had been entered. Accordingly, the Examiner was contacted by telephone on March 15, 2006, and the Examiner indicated that the Amendment will be entered, and this indication has been made of record in the Record of Interview filed April 12, 2006.

The Amendment Under 37 C.F.R. 1.116 canceled claims 10, 11, 12, 15, 26-21, 35 and 36, so that the remaining claims under rejection are claims 16-23, 32-34 and 37.

(V) SUMMARY OF THE CLAIMED SUBJECT MATTER

The following description is made with respect to the independent claim and includes references to particular parts of the specification. As such, the following is merely exemplary and is not a surrender of other aspects of the present invention that are also enabled by the present specification and that are directed to equivalent structures or methods within the scope of the claims.

The sole independent claim, i.e., claim 16, recites a liposome comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups (page 7, line 17 to page 18, line 10) and a separately bonded antibody bound to the liposome through thioether groups (page 8, line 18 to page 10, line 7), said liposome comprising lipids whose partial component has maleimidated terminal (page 5, beginning at line 1), and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid (page 8, lines11-17), and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome (page 9, beginning at line 25), and said antibody comprising a GAH antibody (page 8, beginning at the fourth line from the bottom).

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(a) Claims 16-23 and 32-34 are rejected under 35 U.S.C.102(b) as being anticipated by Tagawa, U.S. Patent No. 5,264,221 (hereinafter "Tagawa '221").

(b) Claims 16-23, 32-34 and 37 are rejected under 35 U.S.C.103(a) as being unpatentable over Tagawa '221.

(c) Claims 16-23, 32-34 and 37 are rejected under 35 U.S.C.103(a) as being unpatentable over Kirpotin et al., Biochemistry, 1997 (hereinafter "Kirpotin"), in combination with Tagawa '221.

(d) Claims 16-23, 32-34 and 37 are rejected under 35 U.S.C.103(a) as being unpatentable over Hosakawa, U.S. Patent No. 6,787,153 (hereinafter "Hosakawa '153"), or Hosakawa, U.S. Patent No. 6,139,869 (hereinafter "Hosakawa '869").

(e) Claims 16-23, 32-34 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of Hosakawa '153.

(f) Claims 16-23, 32-34 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of Hosakawa '869.

(VII) ARGUMENT

(a) Traversal of rejection of claims 16-23 and 32-34 under 35 U.S.C. § 102(b) as being anticipated by Tagawa, U.S. Patent No. 5,264,221 (hereinafter "Tagawa '221").

(A) Rejection of Claim 16

The rejection of claim 16 under 35 U.S.C. § 102(b) as being anticipated by Tagawa is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that independent claim 16 is directed to a liposome comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody. Thus, Appellants' independent claim 16 includes, amongst other features, that an amount of the bonded compound is 15 to 30 mole% and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome.

Appellants submit that the anticipation rejection of claim 16 does not allege that Tagawa '221 teaches each and every feature recited in Appellants' claim 16 whereby the

rejection is without appropriate basis. The rejection makes allegations regarding canceled independent claim 10, but does not indicate how Tagawa '221 anticipates Appellants' independent claim 16. The rejection does not provide support for an anticipation rejection by specifically pointing out where each and every feature recited in Appellants' claim 16 is disclosed in Tagawa '221. In fact, the Examiner has also made an obviousness rejection utilizing this same document, and this obviousness rejection is evidence of a lack of anticipation because the same claim is separately rejected under 35 U.S.C. 103(a) due to differences between Appellants' claimed invention and the disclosure of Tagawa '221. Accordingly, for at least this basis the rejection is without appropriate basis and should be withdrawn.

With regard to the disclosure of Tagawa '221, Appellants submit that Tagawa '221 discloses the use of a thiolated antibody in a ratio of 0.1 mol% to 20 mol% based on 1 mol of maleimide group (column 4, lines 9 to 7 from the bottom). Also, Tagawa '221 discloses in Example 3, a PEG modified liposome bound with an antibody. As explained in Example 3 of Tagawa '221, the liposome disclosed in Example 3 was prepared according to the method described in Example 2, which means that 100 mg of lipid was used for preparation of the liposome of Example 3. Moreover, in contrast to the liposomes recited in Appellants' independent claim 16, Tagawa '221 discloses in Example 2 (at column 7, lines 43-44) the preparation of a liposome by using 5 mg of Fb' antibody for 100 mg of lipids. Thus, Example 2 of Tagawa '221 discloses the use of 5 mg antibody per 100 mg of lipids.

The Examiner points to a broader range disclosed by Tagawa '221 and also contends that 4.5 is close to 5. However, such disclosure should not be considered to be anticipation and is not applicable to **Appellants' claim 16 which recites that an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome**. As stated in MPEP 2131.03, Rev.2, May 2004, II. PRIOR ART WHICH TEACHES A RANGE WITHIN, OVERLAPPING, OR TOUCHING THE CLAIMED RANGE ANTICIPATES IF THE PRIOR ART RANGE DISCLOSES THE CLAIMED RANGE WITH "SUFFICIENT SPECIFICITY", When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." For example, if the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims.

In the instant situation, Appellants respectfully submit that there is not sufficient specificity so as to comprise anticipation and the claimed invention is not clearly envisaged in Tagawa '221. This lack of anticipation is also readily evident from the unexpected results associated with Appellants' invention as will be discussed below.

Still further, as stated in MPEP 2131.03, Rev.2, May 2004, III. PRIOR ART WHICH TEACHES A VALUE OR RANGE THAT IS VERY CLOSE TO, BUT DOES NOT OVERLAP OR TOUCH, THE CLAIMED RANGE DOES NOT ANTICIPATE THE CLAIMED RANGE, "[A]nticipation under § 102 can be found only when the reference discloses exactly what is claimed and that where there are differences between the reference disclosure and the claim, the rejection must be based on § 103 which takes differences into account." Accordingly, anticipation cannot be present when, in the instant situation, the values to do overlap or touch.

Moreover, the claimed invention relates to liposome modified with the specified amount of the antibody as mentioned above and also modified with a specified amount of a bonded compound containing a polyalkylene glycol moiety, i.e., 15 to 30 mole%. Tagawa '221 fails to teach or suggest the claimed range of polyethylene glycol in combination with the specified amount of antibody.

Thus, Appellants respectfully submit that Tagawa '221 does not teach each and every element as recited in Appellants' claims whereby the anticipation rejection is without appropriate basis. In particular, as noted above, the Examiner has also made an obviousness rejection utilizing this same document, and this obviousness rejection is evidence of a lack of anticipation because the same claim is separately rejected under 35 U.S.C. 103(a) due to differences between Appellants' claimed invention and the disclosure of Tagawa '221. For example, Appellants note that the obviousness rejection specifically states that, "Tagawa's does not teach the entire claimed range of the bonded compound and the bonded antibody."

Expanding upon differences between Appellants' claimed subject matter and Tagawa '221, Appellants emphasize that throughout their originally filed application patentable differences are set forth over the disclosure of Tagawa '221. In this regard, attention is directed to Appellants' specification at page 2, first full paragraph wherein the subject matter of Tagawa '221 is contrasted with reference being made to the 5 mg addition of antibodies as noted above in Example 2 of Tagawa '221.

Moreover, beginning in the next paragraph on page 2 of Appellants' specification and continuing through page 3, the advantages of Appellants' invention are further discussed.

Also, the unexpected advantages of using a smaller amount of bound antibody according to Appellants' invention is also apparent from a review of Appellants' Example 4. **As explained in Example 4, a smaller amount of bound antibody gives a higher therapeutic effect, and this result is unexpected by one of ordinary skill in the art in view of Tagawa '221 which discloses the use of a larger amount of bound antibody than the presently claimed liposome, medicament composition and method.**

Regarding the unexpected results, Appellants note that the claimed subject matter provides for the achieving of remarkable suppressive effect against tumor proliferation and superior retention in blood as compared with the liposome with 5 mg antibody per 100 mg lipids as disclosed in 'Tagawa 221 Appellants' originally filed specification, including Example 4, provides evidence of the unexpectedly advantageous results

associated with Appellants' invention, In particular, in Example 4, liposomes 2-7 containing varying amounts of GAH antibody (0.5, 1.2, 2.0, 4.5, 5.3 and 11.4 mg) bonded to 100 mg of the total lipids of the liposome encapsulating doxorubicin (DXR, also referred to as adriamycin) were prepared according to the method of Example 1. Also, liposomes 1 bonded with no antibody were prepared. For convenience Table 3 from Appellants' specification including the content of the liposomes in the specification is reproduced below and modified to include conversion to amount of bound PEG (per 1 mol of maleimidated lipids). A discussion regarding the calculations regarding the conversion will be presented following the discussion of Example 4.

Liposome disclosed in Example 4	Amount of bonded antibodies (mg/100 mg lipids)	Amount of included DXR (mg/100 mg lipids)	Amount of bonded PEG (mg/100 mg lipids)	Amount of bound PEG (per 1 mol of maleimidated lipids
1	0	9.5	8.2	28 mol%
2	0.5	9.1	8.2	28 mol%
3	1.2	9.5	8.1	28 mol%
4	2.0	8.9	5.3	18 mol%
5	4.5	9.6	6.2	21 mol%
6	5.3	9.7	6.4	22 mol%
7	11.4	10.0	3.2	11 mol%
Tagawa '221	Fab' antibody 5 mg			47 mol%

Example 4 further notes that retention of each liposome in blood was equivalent within the range of the amount of PEG bonded (> 4.4 mg/100 mg lipids), and Example 4 therefore indicates that the experimental results shown in the examples depended on the bonded amount of antibodies.

In Example 4, stomach cancer cell strain MKN45 was subcutaneously transplanted at two sites on nude mice. For the "efficacy test", administrations of liposomes with different amounts of bonded antibodies were started when the tumor reached to a size large enough to measure its long and short diameters. The dose of the liposomes was 5.0 mg/kg (as the amount of DXR) per administration, and a DXR-administered group (5.0 mg/kg) was provided as a positive control, and physiological saline was administered to the control group.

Significant inhibitory effects against tumor proliferation were found in all of the treated groups compared with the control group. A review of Fig. 3 in Appellants' application, when comparison is made to the DXR-administered group, reveals significant inhibitory effects against tumor proliferation in the samples with the amounts of bonded antibodies within the range of 0.5 to 5.3 mg/100 mg of total lipids. The inhibitory activity against tumor proliferation was observed with a peak in the vicinity of 2 mg/100 mg of total lipids as the amount of bonded antibodies.

In the "pharmacokinetic test", liposomes 4 to 7 with different amounts of bonded antibodies (2.0, 4.5, 5.3 and 11.4 mg/100 mg of total lipids) were intravenously administered to mice (each group consisted of 2 or 3 mice, 1.0 mg/kg as the amount of DXR amount). Four hours after the administration, blood plasma was collected from each animal. The amount of DXR in plasma was measured by the fluorescence measurement method in the same manner as in Example 2. The amounts of DXR in plasma in the respective samples after the administration were compared to find correlation between the amount of bonded antibodies and the retention in blood of the liposomes

encapsulating DXR and bonded with antibodies. In the pharmacokinetic test, correlation between the DXR amount in plasma after administration of each sample and the amount of bonded antibodies of each sample was obtained for samples having the amount of the bonded antibodies of 2 mg/100 mg of lipids or more, as can be seen from a review of Fig.4 in Appellants' application. As a result, it was found that, when the amount of the bonded antibodies exceeded 2 mg/100 mg of the lipids, the retention in blood decreased depending on the increasing amount of the bonded antibodies.

The conversion to amount of bound PEG (per 1 mol of maleimidate lipids) shown in the Table above can be calculated as follows. For example, liposome 1 shown in Table 3 is indicated to have the bonded PEG of 8.2 mg/100 mg lipids. The PEG used in Example 4 has the molecular weight of 10,000, which will be explained below, and therefore, the bonded PEG is 0.82 μ mol/100 mg lipids. The amount of maleimidated lipid per 100 mg lipids is 2.9 μ mol, which will also be explained below. Accordingly, the amount of bound PEG per 1 mole of maleimidated lipid is calculated as:

0.82 μ mol ÷ 2.9 μ mol x 100(%) = 28 mol%.

The amounts of the bound antibody and the bound PEG in the liposome disclosed in Tagawa '221 are 5 mg/100 mg lipids and 47 mol% per I mol of maleimidated lipids, respectively.

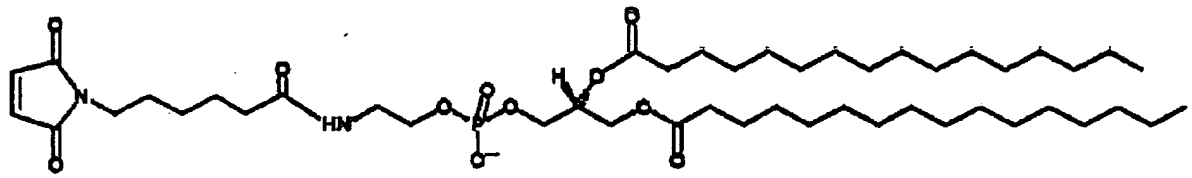
Further, regarding the conversion and as noted above, the liposomes disclosed in Example 4 were prepared according to the method of Example 1, as explained at page 17, line 2 in Appellants' specification. The liposome of Example 1 consisted of a mixture of dipalmitoylphosphatidylcholine (DPPC, M.W. 734, 18 moles), cholesterol (Cho, M.W.

346.7, 10 moles), and ε-maleimidocaproyldipalmitoylphosphatidylethanolamine (MC-DPPE, M.W. 884, 0.5 mol). The content of MC~DPPE in the total lipid can be calculated as follows:

DPPC	:	Cho	:	MCDPPE
18 mol		10 mol		0.5 mol
18 x 734		10 x 346.7		0.5 x 884
13212(A)		3467(B)		442(C)

A+B+C (g) : C (g) = 100 (mg) : Y(g)
Y(g) = 2.58mg → 2.58mg ÷ 442 = 2.9 μmol

Structure of MC-DPPE (M.W. 884)



With regard to the molecular weights of the PEGs, a two-chain type PEG which is referred to as "PEG 2000" and a two-chain type PEG which is referred to as "PEG 5000" were used in the Examples. Specifically, the explanation of "thiolated PEG (30 mg/mL, a two-chain type PEG having a molecular weight of 2000 (PEG 2000) and a two-chain type PEG having a molecular weight of 5000 (PEG 5000))" is given in Appellants' specification at page 12, lines 3 to 1 from the bottom.

A specification for "PEG 5000" which was attached to a product purchased on behalf of Appellants (Exhibit 1 attached thereto). In this specification, the product was named as "Sun-Bright SHPEG2" by a manufacturer, and as a result of quality test, the

product was found to have a molecular weight of 11,000 which is within the standardized range of 10,900 to 13,000 specified by the manufacturer.

Accordingly, unexpected results are shown for the liposome recited in Appellants' independent claim 16 comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(B) Rejection of Claim 17

The rejection of claim 17 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 17 is dependent upon and includes the subject matter recited in claim 16. Therefore, the anticipation rejection based upon claim 17 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 17, which further includes that the liposome is obtained by reacting a maleimide

group of the maleimidated lipid with the compound containing a polyalkylene glycol moiety introduced with a thiol group.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(C) Rejection of Claim 18

The rejection of claim 18 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 18 is dependent upon and includes the subject matter recited in claim 16. Therefore, the anticipation rejection based upon claim 18 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 18, which further includes that the compound is bonded to a surface of the liposome.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(D) Rejection of Claim 19

The rejection of claim 19 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 19 is dependent upon and includes the subject matter recited in claim 16. Therefore, the anticipation rejection based upon claim 19 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 19, which further includes that the polyalkylene glycol is polyethylene glycol.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(E) Rejection of Claim 20

The rejection of claim 20 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 20 is dependent upon claim 19, and includes the subject matter recited in claims 16 and 19. Therefore, the anticipation rejection based upon claim 20 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 19.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 20, which further includes that the compound has two polyalkylene glycol groups.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(F) Rejection of Claim 21

The rejection of claim 21 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 21 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the anticipation rejection based upon claim 21 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 21, which further includes that each polyethylene glycol group has a molecular weight of 2,000 to 7,000 daltons.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(G) Rejection of Claim 22

The rejection of claim 22 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 22 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the anticipation rejection based upon claim 21 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 22, which further includes that each polyethylene glycol group has a molecular weight of 5,000 daltons.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(H) Rejection of Claim 23

The rejection of claim 23 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 23 is dependent upon and includes the subject matter recited in claim 16. Therefore, the anticipation rejection based upon claim 23 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 23, which further includes that it is a liposome obtained by reacting a liposome having a maleimide group and a sulfur-containing group deriving from the antibody to form a thioether bond.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(I) Rejection of Claim 32

The rejection of claim 32 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 32 is dependent upon and includes the subject matter recited in claim 16. Therefore, the anticipation rejection based upon claim 32 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 32, which further includes a medicament composition for treatment of cancer comprising the liposome according to claim 16 and a medicament effective for treatment of cancer.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(J) Rejection of Claim 33

The rejection of claim 33 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 33 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the anticipation rejection based upon claim 33 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 33, which further includes that the cancer is stomach cancer or colon cancer.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(K) Rejection of Claim 34

The rejection of claim 34 under 35 U.S.C. § 102(b) as being anticipated by Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 34 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the anticipation rejection based upon claim 34 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Tagawa '221 does not teach the combination of features as recited in claim 34, which further includes a method for treatment of cancer which comprises administering to a patient the medicament composition according to claim 32.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(b) Traversal of rejection of claims 16-23, 32-34 and 37 under 35 U.S.C.103(a) as being unpatentable over Tagawa '221.

(A) Rejection of Claim 16

The rejection of claim 16 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants once again note that independent claim 16 is directed to a liposome comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody. Thus, Appellants' independent claim 16 includes, amongst other features, that an amount of the bonded compound is 15 to 30 mole% and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome.

Initially, Appellants submit that the obviousness rejection is without appropriate basis in that the rejection does not indicate how Tagawa '221 is being modified to arrive at Appellants' recited subject matter, including amongst other features, **an amount of the**

bonded compound is 15 to 30 mole% and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome.

The rejection merely contends that:

> From these teachings, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of the thiol activated antibody, since this amount depends upon the amount of the corresponding receptors on/in the host cell and then block the rest of the maleimide groups on the liposomes with the thiol modified PEG. Instant invention therefore, is deemed to be an obvious extension of prior art teachings.

Moreover, the rejection contends that:

> These arguments are not persuasive. A careful review of instant Fig. 2 which shows the concentration of DXR in plasma plateaus at 15 mole percent and therefore, one would except the same values of DXR even beyond 30 mole percent, that is at the PEG mole percentages in the prior art. Applicant has not shown any unexpected results and therefore, the rejection is maintained.

In contrast, to the Examiner's assertions, there is no motivation to modify Tagawa '221 to provide a liposome, including amongst other features recited in the claim, an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome. Moreover, in contrast to the assertions in the Final Office Action, Appellants have show unexpected results for the claimed subject matter, as presented in the arguments above with respect to the anticipation rejection based upon Tagawa '221.

For the sake of brevity, Appellants are not repeating each of the arguments supporting patentability over Tagawa '221 set forth with respect to the anticipation

rejection, and incorporate these arguments herein as if set forth in their entirety. However, it is noted, for example, the unexpected advantages of using a smaller amount of bound antibody according to Appellants' invention is apparent from a review of Appellants' Example 4. As explained in Example 4, a smaller amount of bound antibody gives a higher therapeutic effect, and this result is unexpected by one of ordinary skill in the art in view of Tagawa '221 which discloses the use of a larger amount of bound antibody than the presently claimed liposome, medicament composition and method. The Examiner's rejection does not address Appellants' arguments of unexpected advantages of not only using a smaller amount of bound antibody, but that when the amount of the bonded antibodies exceeded 2 mg/100 mg of the lipids, the retention in blood decreased depending upon the increasing amount of the bonded antibodies.

Accordingly, the anticipation rejection based upon Tagawa '221 should be withdrawn.

(B) Rejection of Claim 17

The rejection of claim 17 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 17 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 17 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 17, which further includes that the liposome is obtained by reacting a maleimide group of the maleimidated lipid with the compound containing a polyalkylene glycol moiety introduced with a thiol group.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(C) Rejection of Claim 18

The rejection of claim 18 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 18 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 18 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 18, which further includes that the compound is bonded to a surface of the liposome.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(D) Rejection of Claim 19

The rejection of claim 19 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 19 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 19 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 19, which further includes that the polyalkylene glycol is polyethylene glycol.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(E) Rejection of Claim 20

The rejection of claim 20 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 20 is dependent upon claim 19, and includes the subject matter recited in claims 16 and 19. Therefore, the obviousness rejection based upon claim 20 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 19.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 20, which further includes that the compound has two polyalkylene glycol groups.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(F) Rejection of Claim 21

The rejection of claim 21 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 21 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the obviousness rejection based upon claim 21 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 21, which further includes that each polyethylene glycol group has a molecular weight of 2,000 to 7,000 daltons.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(G) Rejection of Claim 22

The rejection of claim 22 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 22 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the obviousness rejection based upon claim 22 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 22, which further includes that each polyethylene glycol group has a molecular weight of 5,000 daltons.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(H) Rejection of Claim 23

The rejection of claim 23 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 23 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 23 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 23, which further includes that it is a liposome obtained by reacting a liposome having a maleimide group and a sulfur-containing group deriving from the antibody to form a thioether bond.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(l) Rejection of Claim 32

The rejection of claim 32 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 32 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 32 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 32, which further includes a medicament composition for treatment of cancer comprising the liposome according to claim 16 and a medicament effective for treatment of cancer.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(J) Rejection of Claim 33

The rejection of claim 33 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 33 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 33 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 33, which further includes that the cancer is stomach cancer or colon cancer.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(K) Rejection of Claim 34

The rejection of claim 34 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 34 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 34 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 34, which further includes a method for treatment of cancer which comprises administering to a patient the medicament composition according to claim 32.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(L) Rejection of Claim 37

The rejection of claim 37 under 35 U.S.C. § 103(a) as being unpatentable over Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 37 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 37 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Tagawa '221 does not teach or suggest the combination of features as recited in claim 37, which further includes that the medicament comprises doxorubicin.

Accordingly, the obviousness rejection based upon Tagawa '221 should be withdrawn.

(c) Traversal of rejection of claims 16-23, 32-34 and 37 under 35 U.S.C.103(a) as being unpatentable over Kirpotin in combination with Tagawa '221.

(A) Rejection of Claim 16

The rejection of claim 16 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotiin in combination with Tagawa is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants once again note that independent claim 16 is directed to a liposome comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody. Thus, Appellants' independent claim 16 includes, amongst other features, that an amount of the bonded compound is 15 to 30 mole% and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome.

In this ground of rejection, the Examiner notes the deficiencies of Kirpotin in apparently not disclosing the amount of antibody or the recited antibody, and does not address other features in claim 16, such as the amount of the bonded compound being

15 to 30 mole%, and apparently is attempting in some manner to overcome these deficiencies of Kirpotin utilizing Tagawa '221 to arrive at Appellants' claimed subject matter. The rejection basically contends that in the absence of unexpected results it would have been obvious to one of ordinary skill in the art to vary amounts of since Tagawa shows that one can bind various amounts of antibody to the bilayer forming lipid. The rejection further contends that Appellants have not shown any unexpected results by varying the amounts of antibody and PEG in prior art's teachings.

The deficiencies of Tagawa '221 and unexpected results associated with amounts of components and the subject matter in Appellants' claim 16 is discussed above, and for the sake of brevity are not repeated again but are incorporated by reference in this argument as if set forth in their entirety. In this regard, the rejection based upon Kirpotin relies upon Tagawa '221 in an attempt to arrive at Appellants' claims. However, for the reasons set forth above, there is no teaching or suggestion in Tagawa '221 to arrive at Appellants' claims. Moreover, as noted above, the unexpected results associated with Appellants' claimed subject matter overcomes any *prima facie* case of obviousness even if present.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(B) Rejection of Claim 17

The rejection of claim 17 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally

reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 17 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 17 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 17, which further includes that the liposome is obtained by reacting a maleimide group of the maleimidated lipid with the compound containing a polyalkylene glycol moiety introduced with a thiol group.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(C) Rejection of Claim 18

The rejection of claim 18 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 18 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 18 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 18, which further includes that the compound is bonded to a surface of the liposome.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(D) Rejection of Claim 19

The rejection of claim 19 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 19 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 19 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 19, which further includes that the polyalkylene glycol is polyethylene glycol.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(E) Rejection of Claim 20

The rejection of claim 20 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally

reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 20 is dependent upon claim 19, and includes the subject matter recited in claims 16 and 19. Therefore, the obviousness rejection based upon claim 20 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 19.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 20, which further includes that the compound has two polyalkylene glycol groups.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(F) Rejection of Claim 21

The rejection of claim 21 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 21 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the obviousness rejection based upon claim 21 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 21, which further includes that each polyethylene glycol group has a molecular weight of 2,000 to 7,000 daltons.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(G) Rejection of Claim 22

The rejection of claim 22 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 22 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the obviousness rejection based upon claim 21 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 22, which further includes that each polyethylene glycol group has a molecular weight of 5,000 daltons.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(H) Rejection of Claim 23

The rejection of claim 23 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 23 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 23 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 23, which further includes that it is a liposome obtained by reacting a liposome having a maleimide group and a sulfur-containing group deriving from the antibody to form a thioether bond.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(I) Rejection of Claim 32

The rejection of claim 32 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 32 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 32 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 32, which further includes a medicament composition for treatment of cancer comprising the liposome according to claim 16 and a medicament effective for treatment of cancer.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(J) Rejection of Claim 33

The rejection of claim 33 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 33 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 33 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 33, which further includes that the cancer is stomach cancer or colon cancer.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(K) Rejection of Claim 34

The rejection of claim 34 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 34 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 34 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 34, which further includes a method for treatment of cancer which comprises administering to a patient the medicament composition according to claim 32.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(L) Rejection of Claim 37

The rejection of claim 37 under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin in combination with Tagawa '221 is in error, the decision of the Examiner to finally

reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 37 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 37 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Kirpotin in combination with Tagawa '221 does not teach or suggest the combination of features as recited in claim 37, which further includes that the medicament comprises doxorubicin.

Accordingly, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 should be withdrawn.

(d) Traversal of rejection of claims 16-23, 32-34 and 37 under 35 U.S.C.103(a) as being unpatentable over Hosakawa '153, or Hosakawa '869.

In this ground of rejection, the Examiner notes that Appellants' arguments are not found to be persuasive. The rejection notes that, "Applicant admits on page 26 of the response that KosoKawa 153 and 869 disclose the same amount of antibody and the same amount of PED as Tagawa 221 and therefore, the examiner's response is similar to that for their arguments regarding Tagawa, 221." Thus, as discussed above, the antibody according to the presently claimed invention is defined in Appellants' independent claim 16 as comprising a bonded compound containing a polyalkylene

glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody.

As noted above, the presently claimed liposomes have unexpectedly high suppressive effect against tumor proliferation and superior retention in blood as compared with the liposome with 5 mg antibody per 100 mg lipids disclosed in Tagawa '221. Hosokawa '153 and Hosokawa '869 also disclose the same amount of antibody and the same amount of PEG as Tagawa '221.

For the sake of brevity, Appellants are not repeating each of the arguments as discussed above, but incorporate these arguments as if set forth in their entirety herein.

Accordingly Hosokawa '153 and Hosokawa '869 do not teach or suggest the subject matter recited by Appellants, and rejections based upon these documents should be withdrawn.

(B) Rejection of Claim 17

The rejection of claim 17 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 17 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 17 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 17, which further includes that the liposome is obtained by reacting a maleimide group of the maleimidated lipid with the compound containing a polyalkylene glycol moiety introduced with a thiol group.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(C) Rejection of Claim 18

The rejection of claim 18 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 18 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 18 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 18, which further includes that the compound is bonded to a surface of the liposome.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(D) Rejection of Claim 19

The rejection of claim 19 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 19 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 19 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 19, which further includes that the polyalkylene glycol is polyethylene glycol.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(E) Rejection of Claim 20

The rejection of claim 20 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 20 is dependent upon claim 19, and includes the subject matter recited in claims 16 and 19. Therefore, the obviousness rejection based upon claim 20 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 19.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 20, which further includes that the compound has two polyalkylene glycol groups.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(F) Rejection of Claim 21

The rejection of claim 21 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 21 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the obviousness rejection based upon claim 21 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 21, which further includes that each polyethylene glycol group has a molecular weight of 2,000 to 7,000 daltons.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(G) Rejection of Claim 22

The rejection of claim 22 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 22 is dependent upon claim 20, and includes the subject matter recited in claims 16, 19 and 20. Therefore, the obviousness rejection based upon claim 21 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16, 19 and 20.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 22, which further includes that each polyethylene glycol group has a molecular weight of 5,000 daltons.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(H) Rejection of Claim 23

The rejection of claim 23 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 23 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 23 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 23, which further includes that it is a liposome obtained by reacting a liposome having a maleimide group and a sulfur-containing group deriving from the antibody to form a thioether bond.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn..

(l) Rejection of Claim 32

The rejection of claim 32 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 32 is dependent upon and includes the subject matter recited in claim 16. Therefore, the obviousness rejection based upon claim 32 is without appropriate basis for at least the reasons set forth by Appellants with respect to claim 16.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 32, which further includes a medicament composition for treatment of cancer comprising the liposome according to claim 16 and a medicament effective for treatment of cancer.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(J) Rejection of Claim 33

The rejection of claim 33 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 33 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 33 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 33, which further includes that the cancer is stomach cancer or colon cancer.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(K) Rejection of Claim 34

The rejection of claim 34 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 34 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 34 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 34, which further includes a method for treatment of cancer which comprises administering to a patient the medicament composition according to claim 32.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(L) Rejection of Claim 37

The rejection of claim 37 under 35 U.S.C. § 103(a) as being unpatentable over Hosakawa '153 or Hosakawa '869 is in error, the decision of the Examiner to finally reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellants note that claim 37 is dependent upon claim 32, and includes the subject matter recited in claims 16 and 32. Therefore, the obviousness rejection based upon claim 37 is without appropriate basis for at least the reasons set forth by Appellants with respect to claims 16 and 32.

Moreover, Hosakawa '153 or Hosakawa '869 does not teach or suggest the combination of features as recited in claim 37, which further includes that the medicament comprises doxorubicin.

Accordingly, the obviousness rejection based upon Hosakawa '153 or Hosakawa '869 should be withdrawn.

(e) Claims 16-23, 32-34 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of Hosakawa '153.

Each of claims 16-23, 32-34 and 37 is not properly rejectable for reasons set forth in (d) above, and further indicated below.

For the sake of brevity, Appellants note that this rejection utilizes one of the same documents, i.e., Hosakawa '153 as utilized in the obviousness rejection set forth in (d) above. Therefore, as is shown above, even if the entire disclosure of Hosakawa '153 is used in an obviousness rejection, the rejection is without appropriate basis. In the instant rejection, the claims of Hosakawa '153 must be applied in the obviousness-type double patenting rejection, and the claims included in the present rejection must be shown to be obvious over the claims of Hosakawa '153. In making this rejection, the Examiner must show how the claimed subject matter, not the disclosed subject matter, of Hosakawa '153 is being modified to arrive at Appellants' claimed subject matter.

In the instant situation, the rejection does not compare the claims of Hosakawa '153 to the claims under rejection. The rejection merely contends that amounts are deemed obvious manipulable parameters practiced by an artisan and does not address any of Appellants' arguments relating to a lack of obviousness with respect to Appellants' recited amounts and the unexpected results associated with Appellants' claimed subject matter. Accordingly, not only is the rejection of each of the claims, i.e., each of claims

16-23, 32-34 and 37, not appropriate over the entire disclosure of Hosakawa '153, the claims are not obvious over the claims of Hosakawa '153.

Accordingly, for the reasons set forth in (d) above and these additional reasons, the obviousness-type double patenting rejection of each of claims 16-23, 32-34 and 37 is without appropriate basis, and should be withdrawn.

(f) Claims 16-23, 32-34 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of Hosakawa '869.

Each of claims 16-23, 32-34 and 37 is not properly rejectable for reasons set forth in (d) above, and further indicated below.

For the sake of brevity, Appellants note that this rejection utilizes one of the same documents, i.e., Hosakawa '869 as utilized in the obviousness rejection set forth in (d) above. Therefore, as is shown above, even if the entire disclosure of Hosakawa '869 is used in an obviousness rejection, the rejection is without appropriate basis. In the instant rejection, the claims of Hosakawa '869 must be applied in the obviousness-type double patenting rejection, and the claims included in the present rejection must be shown to be obvious over the claims of Hosakawa '869. In making this rejection, the Examiner must show how the claimed subject matter, not the disclosed subject matter, of Hosakawa '869 is being modified to arrive at Appellants' claimed subject matter.

In the instant situation, the rejection does not compare the claims of Hosakawa '869 to the claims under rejection. The rejection merely contends that amounts are deemed obvious manipulable parameters practiced by an artisan and does not address any of Appellants' arguments relating to a lack of obviousness with respect to Appellants' recited amounts and the unexpected results associated with Appellants' claimed subject matter. Accordingly, not only is the rejection of each of the claims, i.e., each of claims 16-23, 32-34 and 37, not appropriate over the entire disclosure of Hosakawa '869, the claims are not obvious over the claims of Hosakawa '153.

Accordingly, for the reasons set forth in (d) above and these additional reasons, the obviousness-type double patenting rejection of each of claims 16-23, 32-34 and 37 is without appropriate basis, and should be withdrawn.

CONCLUSION

Each of claims 16-23, 32-34 and 37 is patentable for the reasons set forth herein. Specifically, the applied art of record does not teach or suggest the combination of features recited in Appellants' claims, and is not combinable in the manner proposed by the Examiner, and as even if it were considered to be properly combined, fails to disclose or suggest the unique combination of features recited in Appellant's claims 16-23, 32-34 and 37. Moreover, Appellants' showing of unexpected results overcome any prima facie case of obviousness even if established. Appellants respectfully request that the Board reverse the decision of the Examiner to reject claims 16-23, 32-34 and 37,and remand the application to the Examiner for withdrawal of the rejection.

Thus, Appellants respectfully submit that each and every pending claim of the present application meets requirements for patentability, and that the present application and each pending claim are allowable over the prior art of record.

Respectfully submitted,
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Attachments: (VIII) Claims Appendix
(IX) Evidence Appendix
(X) Related Proceedings Appendix

(VIII) CLAIMS APPENDIX

CLAIMS ON APPEAL

Claim 16. A liposome comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody.

Claim 17. The liposome according to claim 16, which is obtained by reacting a maleimide group of the maleimidated lipid with the compound containing a polyalkylene glycol moiety introduced with a thiol group.

Claim 18. The liposome according to claim 16, wherein the compound is bonded to a surface of the liposome.

Claim 19. The liposome according to claim 16, wherein the polyalkylene glycol is polyethylene glycol.

Claim 20. The liposome according to claim 19, wherein the compound has two polyethylene glycol groups.

Claim 21. The liposome according to claim 20, wherein each polyethylene glycol group has a molecular weight of 2,000 to 7,000 daltons.

Claim 22. The liposome according to claim 20, wherein each polyethylene glycol group has a molecular weight of about 5,000 daltons.

Claim 23. The liposome according to claim 16, which is a liposome obtained by reacting a liposome having a maleimide group and a sulfur-containing group deriving from the antibody to form a thioether bond.

Claim 32. A medicament composition for treatment of cancer comprising the liposome according to claim 16 and a medicament effective for treatment of cancer.

Claim 33. The medicament composition according to claim 32, wherein the cancer is stomach cancer or colon cancer.

Claim 34. A method for treatment of cancer which comprises administering to a patient the medicament composition according to claim 32.

Claim 37. The medicament composition according to claim 32 wherein the medicament comprises doxorubicin.

(IX) Evidence Appendix

Exhibit 1: Specification for "PEG 5000" (Submitted with Amendment filed February 15, 2006)

(X) Related Proceedings Appendix

None

日本油脂株式会社

Form FA-16

試験成績書

サンプル名：サンプライト SH-PEG2

Distribution of molecular weight

Lot No.：SY-003　　日付 98/4/17

手順書 No.	試験項目	規格 (Standard)	結果 (Result)	記入者
PAM-15	性状	白色～微黄白色粉末	微黄白色粉末	三浜
PAM-15	溶状(A_{400})	<0.01	0.035	三浜
PAM-15	確認試験(1)	適 220～224nmに極大吸収	適	三浜
PAM-15	確認試験(2)	適 標準品と一致	適	三浜
PAM-13	分子量分布	10,000～18,000	11,000	三浜
PAM-13	半値幅	8,000～15,000	9,400～13,600	三浜
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAM-07	低分子 SH 成分比 (mol%)	<1.0	0.4	三浜
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAM-08	EDTA 含有量(%)	0.5～1.5	0.81	三浜
PAM-09	水分含量(%)	<2.0	0.87	三浜
PAM-10	強熱残分(%)	<0.5	0.34	三浜
PAM-12	エンドトキシン (EU/mg)	<0.02	0.0004	三浜

確認者：伊藤智　氏名　QC m.　役職　98/4/17　日付

製造管理者：三浜幸三　氏名　QA m.　役職　98/4/17　日付

Exhibit 1

発行年月日：1997/1/29